BRISTOL-MYERS SQUIBB ONCOLOGY

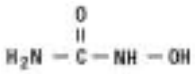
***Rx only***

# HYDREA®
## *(hydroxyurea capsules, USP)*

***DESCRIPTION***

HYDREA® (hydroxyurea capsules, USP) is an antineoplastic agent, available for oral use as capsules providing 500 mg hydroxyurea. Inactive ingredients: citric acid, colorants (D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red 40 and D&C Red 28), gelatin, lactose, magnesium stearate, sodium phosphate, and titanium dioxide.

Hydroxyurea occurs as an essentially tasteless, white crystalline powder. Its structural formula is:



***CLINICAL PHARMACOLOGY***

***Mechanism of Action***

The precise mechanism by which hydroxyurea produces its antineoplastic effects cannot, at present, be described. However, the reports of various studies in tissue culture in rats and humans lend support to the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or of protein. This hypothesis explains why, under certain conditions, hydroxyurea may induce teratogenic effects.

Three mechanisms of action have been postulated for the increased effectiveness of concomitant use of hydroxyurea therapy with irradiation on squamous cell (epidermoid) carcinomas of the head and neck. ***In vitro*** studies utilizing Chinese hamster cells suggest that hydroxyurea (1) is lethal to normally radioresistant S-stage cells, and (2) holds other cells of the cell cycle in the G1 or pre-DNA synthesis stage where they are most susceptible to the effects of irradiation. The third mechanism of action has been theorized on the basis of ***in vitro*** studies of HeLa cells: it appears that hydroxyurea, by inhibition of DNA synthesis, hinders the normal repair process of cells damaged but not killed by irradiation, thereby decreasing their survival rate; RNA and protein syntheses have shown no alteration.

***Pharmacokinetics***

***Absorption***

Hydroxyurea is readily absorbed after oral administration. Peak plasma levels are reached in 1 to 4 hours after an oral dose. With increasing doses, disproportionately greater mean peak plasma concentrations and AUCs are observed.

There are no data on the effect of food on the absorption of hydroxyurea.

***Distribution***

Hydroxyurea distributes rapidly and widely in the body with an estimated volume of distribution approximating total body water.

Plasma to ascites fluid ratios range from 2:1 to 7.5:1. Hydroxyurea concentrates in leukocytes and erythrocytes.

***Metabolism***

Up to 50% of an oral dose undergoes conversion through metabolic pathways that are not fully characterized. In one minor pathway, hydroxyurea may be degraded by urease found in intestinal bacteria. Acetohydroxamic acid was found in the serum of three leukemic patients receiving hydroxyurea and may be formed from hydroxylamine resulting from action of urease on hydroxyurea.

***Excretion***

Excretion of hydroxyurea in humans is a nonlinear process occurring through two pathways. One is saturable, probably hepatic metabolism; the other is first-order renal excretion.

***Special Populations***

***Geriatric, Gender, Race***

No information is available regarding pharmacokinetic differences due to age, gender or race.

***Pediatric***

No pharmacokinetic data are available in pediatric patients treated with hydroxyurea.

**No Revisions**

***Renal Insufficiency***
There are no data that support specific guidance for dosage adjustment in patients with renal impairment. As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of hydroxyurea in patients with renal impairment. Close monitoring of hematologic parameters is advised in these patients.

***Hepatic Insufficiency***
There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

***Drug Interactions***
There are no data on concomitant use of hydroxyurea with other drugs in humans.

***Animal Pharmacology and Toxicology***
The oral $LD_{50}$ of hydroxyurea is 7330 mg/kg in mice and 5780 mg/kg in rats, given as a single dose.

In subacute and chronic toxicity studies in the rat, the most consistent pathological findings were an apparent dose-related mild to moderate bone marrow hypoplasia as well as pulmonary congestion and mottling of the lungs. At the highest dosage levels (1260 mg/kg/day for 37 days then 2520 mg/kg/day for 40 days), testicular atrophy with absence of spermatogenesis occurred; in several animals, hepatic cell damage with fatty metamorphosis was noted. In the dog, mild to marked bone marrow depression was a consistent finding except at the lower dosage levels. Additionally, at the higher dose levels (140 to 420 mg or 140 to 1260 mg/kg/week given 3 or 7 days weekly for 12 weeks), growth retardation, slightly increased blood glucose values, and hemosiderosis of the liver or spleen were found; reversible spermatogenic arrest was noted. In the monkey, bone marrow depression, lymphoid atrophy of the spleen, and degenerative changes in the epithelium of the small and large intestines were found. At the higher, often lethal, doses (400 to 800 mg/kg/day for 7 to 15 days), hemorrhage and congestion were found in the lungs, brain, and urinary tract. Cardiovascular effects (changes in heart rate, blood pressure, orthostatic hypotension, EKG changes) and hematological changes (slight hemolysis, slight methemoglobinemia) were observed in some species of laboratory animals at doses exceeding clinical levels.

***INDICATIONS AND USAGE***
Significant tumor response to HYDREA (hydroxyurea capsules, USP) has been demonstrated in melanoma, resistant chronic myelocytic leukemia, and recurrent, metastatic, or inoperable carcinoma of the ovary.

Hydroxyurea used concomitantly with irradiation therapy is intended for use in the local control of primary squamous cell (epidermoid) carcinomas of the head and neck, excluding the lip.

***CONTRAINDICATIONS***
Hydroxyurea is contraindicated in patients with marked bone marrow depression, i.e., leukopenia (<2500 WBC) or thrombocytopenia (<100,000), or severe anemia.

HYDREA is contraindicated in patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation.

***WARNINGS***
Treatment with hydroxyurea should not be initiated if bone marrow function is markedly depressed (see ***CONTRAINDICATIONS***). Bone marrow suppression may occur, and leukopenia is generally its first and most common manifestation. Thrombocytopenia and anemia occur less often, and are seldom seen without a preceding leukopenia. However, the recovery from myelosuppression is rapid when therapy is interrupted. It should be borne in mind that bone marrow depression is more likely in patients who have previously received radiotherapy or cytotoxic cancer chemotherapeutic agents; hydroxyurea should be used cautiously in such patients.

Patients who have received irradiation therapy in the past may have an exacerbation of postirradiation erythema.

Severe anemia must be corrected before initiating therapy with hydroxyurea.

Erythrocytic abnormalities: megaloblastic erythropoiesis, which is self-limiting, is often seen early in the course of hydroxyurea therapy. The morphologic change resembles pernicious anemia, but is not related to vitamin $B_{12}$ or folic acid deficiency. Hydroxyurea may also delay plasma iron clearance and reduce the rate of iron utilization by erythrocytes, but it does not appear to alter the red blood cell survival time.

Hydroxyurea should be used with caution in patients with marked renal dysfunction.

Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen.

In patients receiving long-term hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia has been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or associated with the patients' underlying disease.

***Carcinogenesis and Mutagenesis***
Hydroxyurea is genotoxic in a wide range of test systems and is thus presumed to be a human carcinogen. In patients receiving long-term hydroxyurea for myeloprolifera-

Fatal and nonfatal pancreatitis have occurred in HIV-infected patients during therapy with hydroxyurea and didanosine, with or without stavudine. Hepatotoxicity and hepatic failure resulting in death have been reported during post-marketing surveillance in HIV-infected patients treated with hydroxyurea and other antiretroviral agents. Fatal hepatic events were reported most often in patients treated with the combination of hydroxyurea, didanosine, and stavudine. Peripheral neuropathy, which was severe in some cases, has been reported in HIV-infected patients receiving hydroxyurea in combination with antiretroviral agents, including didanosine, with or without stavudine.

tive disorders, such as polycythemia vera and thrombocythemia, secondary leukemia has been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or is associated with the patients' underlying disease. Skin cancer has also been reported in patients receiving long-term hydroxyurea.

Conventional long-term studies to evaluate the carcinogenic potential of hydroxyurea have not been performed. However, intraperitoneal administration of 125-250 mg/kg hydroxyurea (about 0.6-1.2 times the maximum recommended human oral daily dose on a mg/m$^2$ basis) thrice weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to control. Hydroxyurea is mutagenic ***in vitro*** to bacteria, fungi, protozoa, and mammalian cells. Hydroxyurea is clastogenic ***in vitro*** (hamster cells, human lymphoblasts) and ***in vivo*** (SCE assay in rodents, mouse micronucleus assay). Hydroxyurea causes the transformation of rodent embryo cells to a tumorigenic phenotype.

***Pregnancy***

Drugs which affect DNA synthesis, such as hydroxyurea, may be potential mutagenic agents. The physician should carefully consider this possibility before administering this drug to male or female patients who may contemplate conception.

HYDREA (hydroxyurea capsules, USP) can cause fetal harm when administered to a pregnant woman. Hydroxyurea is embryotoxic and causes fetal malformations (partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae) at 180 mg/kg/day (about 0.8 times the maximum recommended human daily dose on a mg/m$^2$ basis) in rats and at 30 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m$^2$ basis) in rabbits. Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. Hydroxyurea crosses the placenta. Single doses of ≥375 mg/kg (about 1.7 times the maximum recommended human daily dose on a mg/m$^2$ basis) to rats caused growth retardation and impaired learning ability. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

***PRECAUTIONS***

Therapy with hydroxyurea requires close supervision. The complete status of the blood, including bone marrow examination, if indicated, as well as kidney function and liver function should be determined prior to, and repeatedly during, treatment. The determination of the hemoglobin level, total leukocyte counts, and platelet counts should be performed at least once a week throughout the course of hydroxyurea therapy. If the white blood cell count decreases to less than 2500/mm$^3$, or the platelet count to less than 100,000/mm$^3$, therapy should be interrupted until the values rise significantly toward normal levels. Severe anemia, if it occurs, should be managed without interrupting hydroxyurea therapy.

***Carcinogenesis, Mutagenesis, and Impairment of Fertility***

See ***WARNINGS*** for Carcinogenesis and Mutagenesis information.

Impairment of Fertility: Hydroxyurea administered to male rats at 60 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m$^2$ basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

***Pregnancy***

Pregnancy Category D. (See ***WARNINGS***.)

***Nursing Mothers***

Hydroxyurea is excreted in human milk.

Because of the potential for serious adverse reactions with hydroxyurea, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

***Pediatric Use***

Safety and effectiveness in pediatric patients have not been established.

***Drug Interactions***

Prospective studies on the potential for hydroxyurea to interact with other drugs have not been performed.

Concurrent use of hydroxyurea and other myelosuppressive agents or radiation therapy may increase the likelihood of bone marrow depression or other adverse events. (See ***WARNINGS*** and ***ADVERSE REACTIONS***).

Since hydroxyurea may raise the serum uric acid level, dosage adjustment of uricosuric medication may be necessary.

***Information for Patients***

HYDREA is a medication that must be handled with care. People who are not taking HYDREA should not be exposed to it. If the powder from the capsule is spilled, it should be wiped up immediately with a damp disposable towel and discarded in a closed container, such as a plastic bag.

~~Although h~~Hydroxyurea is not indicated for the treatment of HIV infection~~.~~; however, if HIV-infected patients are treated with hydroxyurea, and in particular, in combination with didanosine and/or stavudine, close monitoring for signs and symptoms of pancreatitis and hepatotoxicity is recommended. Patients who develop signs and symptoms of pancreatitis or hepatotoxicity should permanently discontinue therapy with hydroxyurea. (See ***WARNINGS*** and ***ADVERSE REACTIONS*** sections.)

The medication should be kept away from children and pets.

***ADVERSE REACTIONS***

Adverse reactions have been primarily bone marrow depression (leukopenia, anemia, and occasionally thrombocytopenia), and less frequently gastrointestinal symptoms (stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation), and dermatological reactions such as maculopapular rash, skin ulceration, dermatomyositis - like skin changes, peripheral, and facial erythema. Hyperpigmentation, atrophy of skin and nails, scaling and violet papules have been observed in some patients after several years of long-term daily maintenance therapy with HYDREA. Skin cancer has been reported. Dysuria and alopecia occur very rarely. Large doses may produce moderate drowsiness. Neurological disturbances have occurred extremely rarely and were limited to headache, dizziness, disorientation, hallucinations, and convulsions. HYDREA (hydroxyurea capsules, USP) occasionally may cause temporary impairment of renal tubular function accompanied by elevations in serum uric acid, BUN, and creatinine levels. Abnormal BSP retention has been reported. Fever, chills, malaise, edema, asthenia, and elevation of hepatic enzymes have also been reported.

**(Delete comma)**

Adverse reactions observed with combined hydroxyurea and irradiation therapy are similar to those reported with the use of hydroxyurea or radiation treatment alone. These effects primarily include bone marrow depression (anemia and leukopenia), gastric irritation, and mucositis. Almost all patients receiving an adequate course of combined hydroxyurea and irradiation therapy will demonstrate concurrent leukopenia. Platelet depression (<100,000 cells/$mm^3$) has occurred rarely and only in the presence of marked leukopenia. HYDREA may potentiate some adverse reactions usually seen with irradiation alone, such as gastric distress and mucositis.

The association of hydroxyurea with the development of acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever and dyspnea has been rarely reported. Pulmonary fibrosis also has been reported rarely.

Fatal and nonfatal pancreatitis and hepatotoxicity, and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxyurea in combination with antiretroviral agents, in particular, didanosine plus stavudine (~~see ***WARNINGS*** and ***PRECAUTIONS***~~). Patients treated with hydroxyurea in combination with didanosine, stavudine, and indinavir in study ACTG 5025 showed a median decline in CD4 cells of approximately 100/$mm^3$. (See ***WARNINGS*** and ***PRECAUTIONS.***)

***OVERDOSAGE***

Acute mucocutaneous toxicity has been reported in patients receiving hydroxyurea at dosages several times the therapeutic dose. Soreness, violet erythema, edema on palms and soles followed by scaling of hands and feet, severe generalized hyperpigmentation of the skin, and stomatitis have also been observed.

***DOSAGE AND ADMINISTRATION***

Procedures for proper handling and disposal of antineoplastic drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Because of the rarity of melanoma, resistant chronic myelocytic leukemia, carcinoma of the ovary, and carcinomas of the head and neck in pediatric patients, dosage regimens have not been established.

All dosage should be based on the patient's actual or ideal weight, whichever is less. Concurrent use of HYDREA with other myelosuppresive agents may require adjustment of dosages.

***SOLID TUMORS***

***Intermittent Therapy***

80 mg/kg administered orally as a ***single dose*** every ***third*** day

***Continuous Therapy***

20 to 30 mg/kg administered orally as a ***single dose daily***

***Concomitant Therapy with Irradiation***

***Carcinoma of the head and neck***—80 mg/kg administered orally as a ***single dose*** every ***third*** day

Administration of hydroxyurea should begin at least seven days before initiation of irradiation and continued during radiotherapy as well as indefinitely afterwards provided that the patient may be kept under adequate observation and evidences no unusual or severe reactions.

***RESISTANT CHRONIC MYELOCYTIC LEUKEMIA***

Until the intermittent therapy regimen has been evaluated, CONTINUOUS therapy (20 to 30 mg/kg administered orally as a ***single dose daily***) is recommended.

An adequate trial period for determining the antineoplastic effectiveness of hydroxyurea is six weeks of therapy. When there is regression in tumor size or arrest in tumor growth, therapy should be continued indefinitely. Therapy should be interrupted if the white blood cell count drops below 2500/$mm^3$, or the platelet count below 100,000/$mm^3$. In these cases, the counts should be re-evaluated after three days, and therapy resumed when the counts return to acceptable levels. Since the hematopoietic rebound is prompt, it is usually necessary to omit only a few doses. If prompt rebound has not occurred during combined HYDREA (hydroxyurea capsules, USP) and irradiation therapy, irradiation may also be interrupted. However, the need for postponement of irradiation has been rare; radiotherapy has usually been continued using the recommended dosage and technique. Severe anemia, if it occurs, should be corrected without interrupting hydroxyurea therapy. Because hematopoiesis may be compromised by extensive irradiation or by other antineoplastic agents, it is recommended that hydroxyurea be

administered cautiously to patients who have recently received extensive radiation therapy or chemotherapy with other cytotoxic drugs.

Pain or discomfort from inflammation of the mucous membranes at the irradiated site (mucositis) is usually controlled by measures such as topical anesthetics and orally administered analgesics. If the reaction is severe, hydroxyurea therapy may be temporarily interrupted; if it is extremely severe, irradiation dosage may, in addition, be temporarily postponed. However, it has rarely been necessary to terminate these therapies.

Severe gastric distress, such as nausea, vomiting, and anorexia, resulting from combined therapy may usually be controlled by temporary interruption of hydroxyurea administration.

***Renal Insufficiency***

There are no data that support specific guidance for dosage adjustments in patients with renal impairment. As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of HYDREA in patients with renal impairment. Close monitoring of hematologic parameters is advised in these patients.

***Hepatic Insufficiency***

There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

***HOW SUPPLIED***

HYDREA® (hydroxyurea capsules, USP)

***500 mg capsules*** in bottles of 100 (NDC 0003-0830-50).

Capsule identification number: 830.

***Storage***

~~Store at room temperature; avoid excessive heat.~~ Keep tightly closed.

Store at 25 ° C (77 ° F); excursions permitted to 15 ° - 30 ° C (59 ° - 86 ° F) [see USP Controlled Room Temperature].

***REFERENCES***


1. Recommendations for the Safe Handling of Parenteral Antineoplas-tic Drugs. ***NIH Publications*** No. 83-2621. For sale by the Super-intendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
2. AMA Council Report: Guidelines for Handling Parenteral Antineoplastics. ***JAMA*** 1985; 253 (11): 1590-1592.
3. ***National Study Commission on Cytotoxic Exposure***—Recommen-dations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, ***Massachusetts College of Pharmacy and Allied Health Sciences***, 179 Longwood Avenue, Boston, MA 02115.
4. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. ***Med J Australia*** 1983; 1:426-428.
5. Jones RB, ***et al***: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center, ***CA- A Cancer Journal for Clinicians*** 1983; (Sept./Oct.) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. ***Am J Hosp Pharm*** 1990; 47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA WORK PRACTICE GUIDELINES). ***Am J Health-Syst Pharm*** 1996; 53:1669-1685.



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BRISTOL LABORATORIES
ONCOLOGY PRODUCTS

***Rx only***

# *DROXIA*®
## *(hydroxyurea capsules, USP)*

***WARNING***

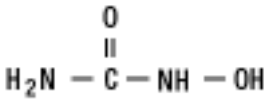
Treatment of patients with DROXIA may be complicated by severe, sometimes life-threatening, adverse effects. DROXIA should be administered under the supervision of a physician experienced in the use of this medication for the treatment of sickle cell anemia.

Hydroxyurea is mutagenic and clastogenic, and causes cellular transformation to a tumorigenic phenotype. Hydroxyurea is thus unequivocally genotoxic and a presumed transspecies carcinogen which implies a carcinogenic risk to humans. In patients receiving long-term hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemias have been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or is associated with the patients' underlying disease. The physician and patient must very carefully consider the potential benefits of DROXIA relative to the undefined risk of developing secondary malignancies.

***DESCRIPTION***

DROXIA® (hydroxyurea capsules, USP) is available for oral use as capsules providing 200 mg, 300 mg and 400 mg hydroxyurea. Inactive ingredients: citric acid, gelatin, lactose, magnesium stearate, sodium phosphate, titanium dioxide and capsule colorants; FD&C Blue #1 and FD&C Green #3 (200 mg capsules); D&C Red #28, D&C Red #33 and FD&C Blue #1 (300 mg capsules); D&C Red #28, D&C Red #33 and D&C Yellow #10 (400 mg capsules).

Hydroxyurea is an essentially tasteless, white crystalline powder. Its structural formula is:



***CLINICAL PHARMACOLOGY***

***Mechanism of Action***

The precise mechanism by which hydroxyurea produces its cytotoxic and cytoreductive effects is not known. However, various studies support the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or of protein.

The mechanisms by which DROXIA produces its beneficial effects in patients with sickle cell anemia

***No Revisions***

## ***Current Insert***

(SCA) are uncertain. Known pharmacologic effects of DROXIA that may contribute to its beneficial effects include increasing hemoglobin F levels in RBCs, decreasing neutrophils, increasing the water content of RBCs, increasing deformability of sickled cells, and altering the adhesion of RBCs to endothelium.

***Pharmacokinetics***

***Absorption***

Hydroxyurea is readily absorbed after oral administration. Peak plasma levels are reached in 1 to 4 hours after an oral dose. With increasing doses, disproportionately greater mean peak plasma concentrations and AUCs are observed.

There are no data on the effect of food on the absorption of hydroxyurea.

***Distribution***

Hydroxyurea distributes rapidly and widely in the body with an estimated volume of distribution approximating total body water.

Plasma to ascites fluid ratios range from 2:1 to 7.5:1. Hydroxyurea concentrates in leukocytes and erythrocytes.

***Metabolism***

Up to 50% of an oral dose undergoes conversion through metabolic pathways that are not fully characterized. In one minor pathway, hydroxyurea may be degraded by urease found in intestinal bacteria. Acetohydroxamic acid was found in the serum of three leukemic patients receiving hydroxyurea and may be formed from hydroxylamine resulting from action of urease on hydroxyurea.

***Excretion***

Excretion of hydroxyurea in humans is a nonlinear process occurring through two pathways. One is saturable, probably hepatic metabolism; the other is first-order renal excretion. In adults with SCA, mean cumulative urinary hydroxyurea excretion was 62% of the administered dose at 8-hours.

***Special Populations***

***Geriatric, Gender, Race***

No information is available regarding pharmacokinetic differences due to age, gender or race.

***Pediatric***

No pharmacokinetic data are available in pediatric patients treated with hydroxyurea for SCA.

***Renal Insufficiency***

There are no data that support specific guidance for dosage adjustment in patients with renal impairment. As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of hydroxyurea in patients with renal impairment. Close monitoring of hematologic parameters is advised in these patients.

***Hepatic Insufficiency***

There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

***Drug Interactions***

There are no data on concomitant use of hydroxyurea with other drugs in humans.

## ***Proposed Revisions***

***No Revisions***

## Current Insert

***Clinical Studies***

The efficacy of hydroxyurea in sickle cell anemia was assessed in a large clinical study (Multicenter Study of Hydroxyurea in Sickle Cell Anemia)[1].

The study was a randomized, double-blind, placebo-controlled trial that evaluated 299 adult patients (≥18 years) with moderate to severe disease (≥3 painful crises yearly). The trial was stopped by the Data Safety Monitoring Committee, after accrual was completed but before the scheduled 24 months of follow-up was completed in all patients, based on observations of fewer painful crises among patients receiving hydroxyurea.

Compared to placebo treatment, treatment with hydroxyurea resulted in a significant decrease in the yearly rate of painful crises, the yearly rate of painful crises requiring hospitalization, the incidence of chest syndrome, the number of patients transfused, and units of blood transfused. Hydroxyurea treatment significantly increased the median time to both first and second painful crises.

Although patients with 3 or more painful crises during the preceding 12 months were eligible for the study, most of the benefit in crisis reduction was seen in the patients with 6 or more painful crises during the preceding 12 months.

| *EVENT* | *HYDROXYUREA (N=152)* | *PLACEBO (N=147)* | *PERCENT CHANGE VS PLACEBO* | *P-VALUE* |
|---|---|---|---|---|
| Median yearly rate of painful crises* | 2.5 | 4.6 | -46 | =0.001 |
| Median yearly rate of painful crises requiring hospitalization | 1.0 | 2.5 | -60 | =0.0027 |
| Median time to first painful crisis (months) | 2.76 | 1.35 | +104 | =0.014 |
| Median time to second painful crisis (months) | 6.58 | 4.13 | +59 | =0.0024 |
| Incidence of chest syndrome (# episodes) | 56 | 101 | -45 | =0.003 |
| Number of patients transfused | 55 | 79 | -30 | =0.002 |
| Number of units of blood transfused | 423 | 670 | -37 | =0.003 |

*A painful crisis was defined in the study as acute sickling-related pain that resulted in a visit to a medical facility, that lasted more than 4 hours, and that required treatment with a parenteral narcotic or NSAID. Chest syndrome, priapism, and hepatic sequestration were also included in this definition.

## Proposed Revisions

**No Revisions**

## Current Insert

No deaths were attributed to treatment with hydroxyurea, and none of the patients developed neoplastic disorders during the study. Treatment was permanently stopped for medical reasons in 14 hydroxyurea-treated (2 patients with myelotoxicity) and 6 placebo-treated patients. (See ***ADVERSE REACTIONS***.)

***Fetal Hemoglobin***

In patients with SCA treated with hydroxyurea, fetal hemoglobin (HbF) increases 4 to 12 weeks after initiation of treatment. In general, average HbF levels correlate with dose and plasma level with possible plateauing at higher dosages.

A clear relation between reduction in crisis frequency and increased HbF or F-cell levels has not been demonstrated. The dose-related cytoreductive effects of hydroxyurea, particularly on neutrophils, was the factor most strongly correlated with reduced crisis frequency.

***INDICATIONS AND USAGE***

DROXIA (hydroxyurea capsules, USP) is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises (generally at least 3 during the preceding 12 months).

***CONTRAINDICATIONS***

DROXIA is contraindicated in patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation.

***WARNINGS***

DROXIA is a cytotoxic and myelosuppressive agent. DROXIA should not be given if bone marrow function is markedly depressed, as indicated by neutrophils below 2000 cells/$mm^3$; a platelet count below 80,000/$mm^3$; a hemoglobin level below 4.5 g/dL; or reticulocytes below 80,000/$mm^3$ when the hemoglobin concentration is below 9 g/dL. Neutropenia is generally the first and most common manifestation of hematologic suppression. (See ***DOSAGE AND ADMINISTRATION***.) Thrombocytopenia and anemia occur less often, and are seldom seen without a preceding leukopenia. Recovery from myelosuppression is usually rapid when therapy is interrupted. DROXIA causes macrocytosis, which may mask the incidental development of folic acid deficiency. Prophylactic administration of folic acid is recommended.

Hydroxyurea should be used with caution in patients with renal dysfunction. (See ***DOSAGE AND ADMINISTRATION***.)

***Carcinogenesis and Mutagenesis***

(See Boxed ***WARNING.***) Hydroxyurea is genotoxic in a wide range of test systems and is thus presumed to be a human carcinogen. In patients receiving long-term hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia has been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or is associated with the patients' underlying disease. Skin cancer has also been reported in patients receiving long-term hydroxyurea.

Conventional long-term studies to evaluate the carcinogenic potential of DROXIA have not been performed. However, intraperitoneal administration of 125-250 mg/kg hydroxyurea (about 0.6-1.2 times the maximum recommended human oral daily dose on a mg/$m^2$ basis) thrice weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to control. Hydroxyurea is mutagenic ***in vitro*** to bacteria, fungi, protozoa, and mammalian cells. Hydroxyurea is clastogenic ***in vitro*** (hamster cells, human lymphoblasts) and ***in vivo*** (SCE assay in rodents, mouse micronucleus assay). Hydroxyurea causes the transformation of rodent embryo cells to a tumorigenic phenotype.

## Proposed Revisions

Fatal and nonfatal pancreatitis have occurred in HIV-infected patients during therapy with hydroxyurea and didanosine, with or without stavudine. Hepatotoxicity and hepatic failure resulting in death have been reported during post-marketing surveillance in HIV-infected patients treated with hydroxyurea and other antiretroviral agents. Fatal hepatic events were reported most often in patients treated with the combination of hydroxyurea, didanosine, and stavudine. Peripheral neuropathy, which was severe in some cases, has been reported in HIV-infected patients receiving hydroxyurea in combination with antiretroviral agents, including didanosine, with or without stavudine.

## Current Insert

***Pregnancy***

DROXIA (hydroxyurea capsules, USP) can cause fetal harm when administered to a pregnant woman. Hydroxyurea is embryotoxic and causes fetal malformations (partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae) at 180 mg/kg/day (about 0.8 times the maximum recommended human daily dose on a mg/m$^2$ basis) in rats and at 30 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m$^2$ basis) in rabbits. Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. Hydroxyurea crosses the placenta. Single doses of ≥375 mg/kg (about 1.7 times the maximum recommended human daily dose on a mg/m$^2$ basis) to rats caused growth retardation and impaired learning ability. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

***PRECAUTIONS***

Therapy with DROXIA requires close supervision. Some patients treated at the recommended initial dose of 15 mg/kg/day have experienced severe or life-threatening myelosuppression, requiring interruption of treatment and dose reduction. The hematologic status of the patient, as well as kidney and liver function should be determined prior to, and repeatedly during treatment. Treatment should be interrupted if neutrophil levels fall to <2000/mm$^3$; platelets fall to <80,000/mm$^3$; hemoglobin declines to less than 4.5 g/dL; or if reticulocytes fall below 80,000/mm$^3$ when the hemoglobin concentration is below 9 g/dL. Following recovery, treatment may be resumed at lower doses (see ***DOSAGE AND ADMINISTRATION***).

Patients must be able to follow directions regarding drug administration and their monitoring and care.

***Carcinogenesis, Mutagenesis, and Impairment of Fertility***

See ***WARNINGS*** and Boxed ***WARNING*** for Carcinogenesis and Mutagenesis information.

Impairment of Fertility: Hydroxyurea administered to male rats at 60 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m$^2$ basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

***Pregnancy***

Pregnancy Category D. (See ***WARNINGS***.)

***Nursing Mothers***

Hydroxyurea is excreted in human milk. Because of the potential for serious adverse reactions with hydroxyurea, a decision should be made either to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

***Pediatric Use***

Safety and effectiveness in pediatric patients have not been established.

***Drug Interactions***

Prospective studies on the potential for hydroxyurea to interact with other drugs have not been performed.

***Information for Patients***

(See ***Patient Information*** at end of labeling). Patients should be reminded that this medication must be handled with care. People who are not taking DROXIA should not be exposed to it. If the powder from the capsule is spilled, it should be wiped up immediately with a damp disposable towel and discarded in a closed container, such as a plastic bag. The medication should be kept away from children and pets.

The necessity of monitoring blood counts every two weeks, throughout the duration of therapy, should be emphasized. For additional information, see the accompanying ***Patient Information*** leaflet.

## Proposed Revisions

~~Although h~~Hydroxyurea is not indicated for the treatment of HIV infection~~.~~; however, if HIV-infected patients are treated with hydroxyurea, and in particular, in combination with didanosine and/or stavudine, close monitoring for signs and symptoms of pancreatitis and hepatotoxicity is recommended. Patients who develop signs and symptoms of pancreatitis or hepatotoxicity should permanently discontinue therapy with hydroxyurea. (See ***WARNINGS*** and ***ADVERSE REACTIONS*** sections.)

## Current Insert

***ADVERSE REACTIONS***

***Sickle Cell Anemia***

In patients treated for sickle cell anemia in the Multicenter Study of Hydroxyurea in Sickle Cell Anemia[1], the most common adverse reactions were hematologic, with neutropenia, and low reticulocyte and platelet levels necessitating temporary cessation in almost all patients. Hematologic recovery usually occurred in two weeks.

Non-hematologic events that possibly were associated with treatment include hair loss, skin rash, fever, gastrointestinal disturbances, weight gain, bleeding and parvovirus B-19 infection; however, these non-hematologic events occurred with similar frequencies in the hydroxyurea and placebo treatment groups. Melanonychia has also been reported in patients receiving DROXIA (hydroxyurea capsules, USP) for SCA.

***Other***

Adverse events associated with the use of hydroxyurea in the treatment of neoplastic diseases, in addition to hematologic effects include: gastrointestinal symptoms (stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation), and dermatological reactions such as maculopapular rash, skin ulceration, dermatomyositis-like skin changes, peripheral erythema and facial erythema. Hyperpigmentation, atrophy of skin and nails, scaling and violet papules have been observed in some patients after several years of long-term daily maintenance therapy with hydroxyurea. Skin cancer has been reported. Dysuria and alopecia occur very rarely. Large doses may produce moderate drowsiness. Neurological disturbances have occurred extremely rarely and were limited to headache, dizziness, disorientation, hallucinations, and convulsions. Hydroxyurea occasionally may cause temporary impairment of renal tubular function accompanied by elevations in serum uric acid, BUN, and creatinine levels. Abnormal BSP retention has been reported. Fever, chills, malaise, edema, asthenia, and elevation of hepatic enzymes have also been reported.

The association of hydroxyurea with the development of acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever and dyspnea has been rarely reported. Pulmonary fibrosis also has been reported rarely.

***OVERDOSAGE***

Acute mucocutaneous toxicity has been reported in patients receiving hydroxyurea at dosages several times the therapeutic dose. Soreness, violet erythema, edema on palms and soles followed by scaling of hands and feet, severe generalized hyperpigmentation of the skin, and stomatitis have been observed.

***DOSAGE AND ADMINISTRATION***

Dosage should be based on the patient's actual or ideal weight, whichever is less. The initial dose of DROXIA is 15 mg/kg/day as a single dose. The patient's blood count must be monitored every two weeks. (See ***WARNINGS*** section.)

If blood counts are in an ***acceptable range****, the dose may be increased by 5 mg/kg/day every 12 weeks until a maximum tolerated dose (the highest dose that does not produce ***toxic**** blood counts over 24 consecutive weeks), or 35 mg/kg/day, is reached.

If blood counts are between the ***acceptable range**** and ***toxic****, the dose is not increased.

If blood counts are considered ***toxic****, DROXIA should be discontinued until hematologic recovery. Treatment may then be resumed after reducing the dose by 2.5 mg/kg/day from the dose associated with hematologic toxicity. DROXIA may then be titrated up or down, every 12 weeks in 2.5 mg/kg/day increments, until the patient is at a stable dose that does not result in hematologic toxicity for 24 weeks. Any dosage on which a patient develops hematologic toxicity twice should not be tried again.

## Proposed Revisions

Fatal and nonfatal pancreatitis and hepatotoxicity, and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxyurea in combination with antiretroviral agents, in particular, didanosine plus stavudine (~~see ***WARNINGS*** and ***PRECAUTIONS***~~). Patients treated with hydroxyurea in combination with didanosine, stavudine, and indinavir in study ACTG 5025 showed a median decline in CD4 cells of approximately 100/mm$^3$. (See ***WARNINGS*** and ***PRECAUTIONS***.)

***acceptable range =***
neutrophils ≥2500 cells/$mm^3$,
platelets ≥95,000/$mm^3$,
hemoglobin >5.3 g/dL and
reticulocytes ≥95,000/$mm^3$ if the hemoglobin concentration <9 g/dL.

****toxic =***
neutrophils <2000 cells/$mm^3$,
platelets <80,000/$mm^3$,
hemoglobin <4.5 g/dL and
reticulocytes <80,000/$mm^3$ if the hemoglobin concentration <9 g/dL.

***Renal Insufficiency***
There are no data that support specific guidance for dosage adjustment in patients with renal impairment. As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of DROXIA in patients with renal impairment. Close monitoring of hematologic parameters is advised in these patients.

***Hepatic Insufficiency***
There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

Procedures for proper handling and disposal of cytotoxic drugs should be considered. Several guidelines on this subject have been published[2-8]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

***HOW SUPPLIED***
DROXIA® (hydroxyurea capsules, USP).

***200 mg capsules*** packaged in HDPE bottles of 60 with a plastic safety screw cap. (NDC 0003-6335-17). The cap and body are opaque blue-green. The capsule is marked in black ink on both the cap and body with ***DROXIA*** and ***6335***.

***300 mg capsules*** packaged in HDPE bottles of 60 with a plastic safety screw cap. (NDC 0003-6336-17). The cap and body are opaque purple. The capsule is marked in black ink on both the cap and body with ***DROXIA*** and ***6336***.

***400 mg capsules*** packaged in HDPE bottles of 60 with a plastic safety screw cap. (NDC 0003-6337-17). The cap and body are opaque reddish-orange. The capsule is marked in black ink on both the cap and body with ***DROXIA*** and ***6337***.

***Storage***
Store at 25° C (77° F); excursions permitted to 15–30° C (59–86° F). Keep tightly closed.

[see USP Controlled Room Temperature]

***REFERENCES***
1. Charache S, ***et al***; Hydroxyurea and Sickle Cell Anemia: Clinical Utility of a Myelosuppressive "Switching" Agent. ***Medicine***. 1996; 75:300-326.
2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. ***NIH Publications***. No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
3. AMA Council Report: Guidelines for Handling Parenteral Antineoplastics. ***JAMA.*** 1985;253(11):1590-1592.

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4. National Study Commission on Cytotoxic Exposure–Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, ***National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences.*** 179 Longwood Avenue, Boston, MA 02115.
5. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. ***Med J Australia.*** 1983;1:426-428.
6. Jones RB, ***et al***: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center, ***CA- A Cancer Journal for Clinicians.*** 1983;(Sept./Oct.) 258-263.
7. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. ***Am J Hosp Pharm.*** 1990;47:1033-1049.
8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), ***Am J Health-Syst Pharm.*** 1996;53:1669-1685.



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***No Revisions***

## ***Current Insert***

## ***Patient Information About***

# ***DROXIA® Capsules***

## ***(generic name = hydroxyurea)***

***What is the most important information I should know about DROXIA?***

DROXIA (pronounced drock-SEE-yuh) capsules are used to treat sickle cell anemia in adults. DROXIA reduces the frequency of painful crises and reduces the need for blood transfusions.

- It is VERY IMPORTANT that you have regular blood counts so that your doctor can decrease or increase the DROXIA dose as needed to avoid serious complications.
- The most serious side effects of DROXIA involve the blood and may include severely low white blood cell counts (leukopenia, neutropenia), which can decrease your resistance to infections, severely low red blood cell counts (anemia), or severely low platelet counts (thrombocytopenia), which can cause bleeding. Almost all patients who received DROXIA in clinical studies needed to have their medication stopped for a time to allow their low blood counts to return to acceptable levels.
- If you get pregnant, DROXIA may harm or cause death to your unborn child. You should not become pregnant while taking DROXIA. Make sure you use a contraceptive method. ***Tell your doctor if you become pregnant or plan to become pregnant while taking*** DROXIA.
- DROXIA may decrease the ability of men to father children and women to have children.
- Laboratory tests and reports in humans suggest DROXIA may increase your risk of developing cancer, especially if it is taken for a long time. However, it is still uncertain whether DROXIA causes cancer.

***What is DROXIA?***

DROXIA is a prescription medicine that is used to reduce the frequency of painful crises and reduce the need for blood transfusions in adults with sickle cell anemia. How DROXIA works is not certain but it may work by reducing the number of white blood cells and/or increasing red blood cells that carry fetal hemoglobin (HbF). Fetal hemoglobin may prevent sickling.

***What is Sickle Cell Anemia?***

Sickle cell anemia is an inherited disorder of the red blood cells. Red blood cells carry oxygen to all parts of the body by using a protein called hemoglobin. Normal red blood cells contain only normal hemoglobin and are shaped like indented disks. These cells are very flexible and move easily through small blood vessels.

In sickle cell anemia, the red blood cells contain sickle hemoglobin, which causes them to change to a rigid, spiked shape (sickle shape) after oxygen is released. Sickled cells get

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stuck and form plugs in small blood vessels. These plugs restrict blood flow, causing damage to surrounding tissues resulting in a painful crisis.

Because there are blood vessels in all parts of the body, painful crises can occur anywhere in your body. In addition, sickle cells are trapped and destroyed in the liver and spleen. This results in a shortage of red blood cells (anemia) .

***Will DROXIA cure my Sickle Cell Anemia?***

No. However, DROXIA may help you better control your sickle cell anemia, but it is important to follow your doctor's instructions carefully.

In a study of adults taking recommended doses, daily treatment with DROXIA resulted in fewer painful crises, fewer patients with "acute chest syndrome" (a pneumonia-like condition that leads to difficulty in breathing) and less need for blood transfusions.

***Who should not take DROXIA capsules?***

Do not take DROXIA capsules if you are allergic to any of the ingredients. Besides the active ingredient hydroxyurea, DROXIA capsules contain the following inactive ingredients: citric acid, gelatin, lactose, magnesium stearate, sodium phosphate, titanium dioxide and capsule colorants. Tell your doctor if you think you have ever had an allergic reaction.

If you get pregnant, DROXIA may harm or cause death to your unborn child. You should not become pregnant while taking DROXIA. Make sure you use a contraceptive method. ***Tell your doctor if you become pregnant or plan to become pregnant while taking*** DROXIA.

***How do I take DROXIA capsules?***

Always follow your doctors instructions carefully when taking DROXIA capsules or ***any*** prescription medication. The usual dose of DROXIA may range from as few as one to several capsules per day. DROXIA is usually taken once a day. You should try to take it at the same time each day. Your doctor will determine the proper starting dose of DROXIA for you based on your weight and blood count. The dose will then be increased slowly to your maximum tolerated dose (maximum dose that does NOT produce severely low blood counts). ***Your doctor should measure your blood counts every two weeks after you begin treatment with DROXIA.*** Depending on the results, your dosage may be adjusted or the drug may be stopped for a while.

DROXIA is a medication that ***must*** be handled with care. People who are not taking DROXIA should not be exposed to it. If the powder from the capsule is spilled, it should be wiped up ***immediately*** with a damp disposable towel and discarded in a closed container, such as a plastic bag.

If you accidentally take an overdose of DROXIA capsules, seek medical attention immediately. Contact your doctor, local poison control center, or emergency room.

***What if I miss a dose of DROXIA capsules?***

Try not to miss your dose of DROXIA, but if you do, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and resume your regular dosing schedule. ***Do not take two doses during the same day.*** If you miss more than one dose, call your doctor for instructions.

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***No Revisions***

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***What should I avoid while taking DROXIA capsules?***

Some other medications can increase your risk of experiencing serious side effects from DROXIA. While you are taking DROXIA capsules, you should inform your doctor of all prescription and over-the-counter medicines that you are taking.

In nursing mothers, DROXIA is present in breast milk. Because of the potential for side effects in the newborn, you should discontinue nursing your baby while taking DROXIA.

***What are the possible side effects of DROXIA capsules?***

As with other medicines, DROXIA may cause unwanted effects, although it is not always possible to tell whether such effects are caused by DROXIA, another medication you may be taking, or your sickle cell anemia. ***Any*** side effects or unusual symptoms that you experience should be reported to your doctor, particularly if they persist or are troublesome.

The most serious side effects of DROXIA involve the blood, and may include severely low white blood cell counts (leukopenia, neutropenia), which can decrease your resistance to infections, severely low red blood cell counts (anemia), or severely low platelet counts (thrombocytopenia), which can cause bleeding. Almost all patients who received DROXIA in clinical studies needed to have their medication stopped for a time to allow their low blood counts to return to acceptable levels.

The side effects reported most often by adults with sickle cell anemia participating in studies of DROXIA included hair loss, skin rash, fever, stomach and/or bowel disturbances, weight gain, bleeding, virus infection, and discolored nails (melanonychia), but these were equally common in people getting a placebo (sugar pill).

Skin cancer and leukemia, which can be fatal, have been reported in patients receiving long-term hydroxyurea for conditions other than sickle cell anemia. In laboratory tests DROXIA causes changes in chromosomes and DNA (genetic material) that strongly suggest it can cause cancer in people, especially if it is taken for a long time.

***Are regular blood counts necessary while taking DROXIA capsules?***

***Yes.*** Your doctor should measure your blood counts every two weeks while you are taking DROXIA. Your DROXIA dose will require adjustment based on these regular blood counts. Serious problems can occur if the DROXIA dose is not adjusted on time.

***What else should I know about DROXIA capsules?***

If you have kidney or liver disease, close monitoring of your blood count, kidney and liver function will be required.

Because it may not be possible to detect a deficiency of folic acid in patients taking DROXIA, your doctor may prescribe a folic acid supplement for you.

***What else should I do to control my sickle cell crises?***

Because painful crises can be brought on by factors such as infection, dehydration, worsening anemia, emotional stress, extreme temperature exposure, or ingestion of substances such as alcohol or other recreational drugs, you should be aware of the following general guidelines that will help keep you pain-free:

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—Seek immediate medical attention when a fever develops or signs of infection appear.
—Avoid smoking and drinking more than 1–2 alcoholic beverages a day.
—Drink 8 to 10 glasses of water or other fluid each day.
—Avoid any types of physical exertion that seem to bring on painful crises or other discomfort.
—Avoid extreme temperature changes and dress appropriately in hot and cold weather.

This medicine was prescribed for your particular condition. Do not use DROXIA Capsules for another condition or give it to others. Keep DROXIA Capsules and all medicines out of the reach of children. Discard DROXIA Capsules when they are outdated or no longer needed by flushing the contents of your bottle down the toilet.

This summary does not include everything there is to know about DROXIA Capsules. Medicines are sometimes prescribed for purposes other than those listed in a ***Patient Information*** leaflet. If you have questions or concerns, or want more information about DROXIA Capsules, your physician and pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your doctor. Remember, no written summary can replace careful discussion with your doctor.

This ***Patient Information*** has been approved by the U.S. Food and Drug Administration.

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***What should I know if I am HIV-positive?***
Because of serious, life-threatening side effects associated with DROXIA used in combination with certain medications for HIV, your doctor should closely monitor your pancreas and liver function with frequent physical examinations and laboratory blood tests. Some studies have shown a decrease in the number of CD4 (T-cells) for HIV-positive patients taking DROXIA. Although DROXIA is approved by the U.S. Food and Drug Administration for treating sickle cell anemia, it is not approved for treating HIV infection.